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Long-term follow-up study of vigabatrin in pretreated children with West syndrome

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A multicentre, long-term, open-label, add-on study of vigabatrin was undertaken in 23 pretreated children with infantile spasms. After 3 months of vigabatrin therapy 11 of the 23 patients had become seizure-free. At this time two-thirds of these 11 children still received other antiepileptic drugs (AEDs) in addition to vigabatrin (mostly valproic acid and/or dexamethasone). After a mean follow-up time of $5\frac{1}{4}$ years (range: $4\frac{1}{4}$–$6\frac{1}{2}$) 72% of 18 evaluable patients (two children died, three were lost to follow-up) revealed seizure freedom for at least 1 year. The mean duration of vigabatrin therapy had been $2\frac{1}{2}$ years (range: 2 weeks to $4\frac{3}{4}$ years). Two-thirds of the 18 children continued to take AEDs, three of them undergoing vigabatrin monotherapy. Relapses of infantile spasms had occurred in 14% of the children. The rate of vigabatrin side effects (10%) was low. At follow-up, the EEG of 13 and the 18 patients demonstrated focal or multifocal epileptic discharges. Fifty-five percent had developed another epilepsy (focal epilepsy, secondary generalized epilepsy or myoclonic–astatic epilepsy). With respect to mental functions, three children were normal or slightly retarded, four showed moderate retardation and 11 revealed severe or very severe retardation. This long-term result is comparable to that in ACTH studies with unselected patients. The conclusions are: (1) vigabatrin is an effective drug for the short-term and long-term treatment of refractory infantile spasms; (2) the relapse rate is low; (3) vigabatrin is well tolerated; (4) with respect to secondary epilepsies and mental functions the long-term outcome in these pretreated children is similar to that in earlier studies with ACTH or corticosteroids.

Key words: epilepsy; infantile spasms; West syndrome; vigabatrin.

INTRODUCTION

West syndrome is an age-related generalized epilepsy which usually manifests before the end of the first year of life. This condition is characterized by the triad of infantile spasms as a peculiar type of seizure, the characteristic EEG pattern of hypsarrhythmia and psychomotor retardation or deterioration. Symptomatic West syndrome is associated with multiple aetiological factors. In the idiopathic/cryptogenic cases there is no known underlying cause. The pathogenesis of this condition remains largely unknown.

Since 1958 ACTH and corticosteroids have been reported to be effective drugs for treatment of infantile spasms[1]. This hormone therapy has been the standard treatment of many years. According to numerous therapeutic trials, about 50–80% of cases have shown cessation of seizures and disappearance of the hypsarrhythmic EEG pattern[2]. However, this therapy is associated with frequent side effects, some of which are potentially fatal (e.g. infections and cardiomyopathy). A high relapse rate after discontinuation has been reported, which may range from 30–65%[2]. The severe long-term prognosis for West syndrome was not improved by the hormonal therapy[2].

There is an increasing body of evidence that vigabatrin is a very effective drug in this catastrophic epilepsy. In the first studies it was used as add-on therapy, and 28–71% of refractory cases became seizure-free[3–6]. More recent publications have indicated that vigabatrin as a primary drug seems to be at least as effective as ACTH, the percentage of seizure-free patients ranging between 43% and 68%[7–17]. In one trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis (11 patients each group) all vigabatrin patients became seizure-free[18].

The objective of the present study was to evaluate the long-term efficacy and safety of vigabatrin as add-on therapy in pretreated children with infantile spasms, and to compare the outcome with that from ACTH or corticosteroids as the standard therapy.

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Table 1: Patient characteristics.

Gender:	male 12, female 11
Age at manifestation of infantile spasms (IS), mean (range):	6 months (2–13)
Aetiology	
Cryptogen	4/23 (17%)
Symptomatic	19/23 (83%)
Hypoxic–ischemic encephalopathy	7/19
Microcephalus and/or mental retardation prior to IS	3/19
Congenital hemiparesis	2/19
Post-immunization manifestation of IS	2/19
Aicardi syndrome	2/19
Schizencephaly	1/19
Incontinentia pigmenti	1/19
Walker–Warburg syndrome	1/19

STUDY DESIGN AND PATIENTS

The study was conducted as a prospective multicentre, long-term, open-label study. Inclusion criteria were a firmly established diagnosis according to the criteria of West syndrome and pretreatment with one or more antiepileptic drugs (AEDs), including corticosteroids or ACTH.

Vigabatrin was added to these AEDs. The starting dose of vigabatrin was 50 mg/kg/day with 50 mg/kg/day increments at 3-day to 1-week intervals. Vigabatrin was titrated to response or to a maximal dose of 150 mg/kg/day. In the responders the concomitant AEDs should be withdrawn: vitamin B_6 with a few days, clobazam or clonazepam within a few weeks, ACTH and dexamethasone within 3–6 months, and other AEDs according to general rules of antiepileptic therapy. In seizure-free patients withdrawal of vigabatrin should be started after 2 years of treatment at the earliest.

The protocol was designed in accordance with the Declaration of Helsinki. Informed consent from the parents or tutors was obtained in all cases.

RESULTS

Patient characteristics

The trial was conducted on 23 children attending three paediatric clinics in Berlin from 1989 to 1997. Details of patients included in the study are presented in Table 1.

Their mean age at commencement of vigabatrin therapy was $9\frac{1}{2}$ months (range: $2\frac{1}{2}$–22 months).

Table 2: Pretreatment of the 23 children with West syndrome.

Medication	Patients (N)	Duration of pretreatment
Valproate	6/23	5 mo (2–8)[a]
Valproate plus dexamethasone	4/23[b]	5 mo ($1\frac{1}{2}$–$10\frac{1}{2}$)[a]
Valproate plus clobazam	2/23	2 mo; $2\frac{1}{2}$ mo
Vitamin B_6	5/23[c]	13 d (3–28)[a]
Vitamin B_6 plus valproate	2/23[d]	4 wk; 8 wk
Vitamin B_6 plus clobazam	1/23	4 mo
Vitamin B_6 plus ACTH	1/23	2 mo
ACTH	1/23	3 mo
Clonazepam plus phenobarbitone	1/23	13 mo

N = number of Patients; d = days; wk = weeks; mo = months.
[a] Mean (range).
[b] Including two children with cryptogenic seizures.
[c,d] Including one patient with cryptogenic seizures in each group.

The following drugs had been used either alone or in combination prior to initiation of the vigabatrin therapy: valproic acid (14 patients), vitamin B_6 (5 patients), dexamethasone (4 patients), clobazam (3 patients) and ACTH (2 patients). Table 2 gives more details of the pretreatment.

Efficacy of short-term treatment

After 3 months of vigabatrin treatment complete cessation of spasms was reported in about half the patients (11 of 23 children), the majority of the responders still receiving polytherapy (8 of the 11 patients), mostly vigabatrin plus valproic acid and/or dexamethasone (Table 3). All four children with cryptogenic infantile spasms became seizure-free. By administering a mean vigabatrin dose of about 100 mg/kg/day (range: 50–150 mg/kg/day), seizure freedom was achieved within 1 week in six of the 11 patients, within 2 weeks in eight of these patients and within 5 weeks in all responding children.

Results of long-term vigabatrin treatment

An evaluation of the efficacy of vigabatrin after a mean follow-up time of $5\frac{1}{4}$ years (range: $4\frac{1}{4}$–$6\frac{1}{2}$ years) is shown in Table 4.

At the time of follow-up 13 of the 18 evaluable patients (72%) had been seizure-free for at least 1 year. Three children were lost to follow-up, two children had died (1 patient with Walker–Warburg syndrome, 1 patient with Aicardi syndrome). In six of the 13 seizure-free patients antiepileptic medication was withdrawn after at least a 2-year seizure-free interval. The other seven seizure-free children, and the additional five children with an active epilepsy, continued to receive antiepileptic drug treatment, as the time interval for attempting antiepileptic drug withdrawal was too short or because a secondary epilepsy had occurred.

Table 3: Response after 3 months of vigabatrin treatment.

Vigabatrin therapy	Patients (N)	Seizure-free	Responder rate[a]	No effect
Monotherapy	8/23	3/8 (37.5%)	2/8 (25%)	3/8 (37.5%)
Polytherapy[b]	15/23	8/15 (53%)	5/15 (34%)	2/15 (12%)
Total		11/23 (48%)	7/23 (30%)	5/23 (22%)

N = number of patients.
[a] More than 50% reduction of seizure frequency.
[b] Co-medication: valproic acid, dexamethasone, carbamazepine.

Table 4: Results of long-term treatment of pretreated infantile spasms with vigabatrin.

Follow-up time (mean, range)	$5\frac{1}{4}$ yr ($4\frac{1}{4}$–$6\frac{1}{2}$)
Patients	
Lost to follow-up	3/23
Died	2/23
Evaluable patients	18/23
Efficacy	
Seizure-free patients (at least 1 yr)	13/18 (72%)
AEDs withdrawn	6/18
With AEDs	7/18
Patients with AEDs	12/18 (66%)
AEDs other than vigabatrin (mono- or polytherapy)	8/18 (44%)
Vigabatrin therapy at follow-up	4/18 (22%)
Vigabatrin monotherapy	3/18
Vigabatrin polytherapy	1/18
Duration of vigabatrin therapy	
All patients (mean, range)	$2\frac{1}{2}$ yr (2 wk–$4\frac{3}{4}$ yr)
Patients seizure-free by vigabatrin (mean, range)	$3\frac{3}{4}$ yr ($1\frac{3}{4}$–$4\frac{3}{4}$ yr)
Maximum Vigabatrin dose (mean, range)	101 mg/kg/d (80–150)
Relapses of infantile spasms	3/21 (14%)
Tolerability	
Patients withdrawn due to severe adverse events	0/21
Adverse events	2/21 (10%)
Irritability, hyperactivity	2/21
EEG findings at follow-up	
Normal	4/18 (22%)
Abnormal	14/18 (78%)
Diffuse slowing	1/18
Focal/multifocal epileptic discharges	13/18
Patients with subsequent epilepsies	10/18 (56%)
Focal and/or secondarily generalized seizures	8/18
Myoclonic–astatic epilepsy	2/18
Mental functions	
Normal or slight retardation	3/18 (17%)
Moderate retardation	4/18 (22%)
Severe or very severe retardation	11/18 (61%)

AEDs = antiepileptic drugs; yr = years; wk = weeks.

Table 5: Treatment of infantile spasms with vigabin in comparison with hormonal therapy: long-term outcome.

			Psychomotor development					
Patients (N)	Treatment	Mortality rate N (%)	Normal or slight retardation N (%)	Moderate retardation N (%)	Severe retardation N (%)	Epilepsy N (%)	Follow-up time[a] (yr)	Authors
214	ACTH, dexamethasone	42/214(19)	33/192(17)	20/192(10)	85/192(72)	136/192(71)	10.4 (3–19)	Riikonen[20]
64	ACTH, prednisone	3/64(5)	6/64(10)	14/64(21)	41/64(64)	34/64(53)	4(3/4–10 1/4)	Glaze *et al*[21]
23	Vigabatrin	2/23(9)	3/18(17)	4/18(22)	11/18(61)	10/18(56)	$5\frac{1}{4}$ ($4\frac{1}{4}$–$6\frac{1}{2}$)	This study

N = number of patients.
[a] Mean range.

Four of these 12 children on medication received vigabatrin either in monotherapy (3 children) or polytherapy (1 child). The other eight children were treated by standard antiepileptic drugs (mostly valproic acid and/or carbamazepine).

The mean duration of vigabatrin therapy in all patients was $2\frac{1}{2}$ years (range: 2 weeks–$4\frac{3}{4}$ years). In the patients who became seizure-free with vigabatrin the mean duration of vigabatrin treatment was $3\frac{3}{4}$ years (range: $1\frac{3}{4}$–$4\frac{3}{4}$ years). The mean of the maximally applied dose of vigabatrin during the whole observation time was 101 mg/kg/day (range: 80–150 mg/kg/day). There were three relapses of infantile spasms during the first 6 months of vigabatrin therapy.

The rate of side effects of vigabatrin was low. Two children experienced hyperactivity and irritability during the first months of vigabatrin therapy, which resolved after dose reduction. In no child had vigabatrin to be withdrawn because of side effects.

At the time of follow-up only four of 18 children (22%) had a normal EEG, the great majority showed ongoing focal or multifocal epileptic discharges (13 of 18 patients) and one patient revealed a diffuse slowing.

Ten of the 18 patients (56%) developed subsequent epilepsies, eight patients had epilepsies with focal and/or secondarily generalized seizures and two patients myoclonic–astatic epilepsy. One patient in whom a myoclonic–astatic epilepsy occurred after discontinuation of vigabatrin was treated again with vigabatrin monotherapy and became seizure-free again. In a second patient a myoclonic–astatic epilepsy manifested during vigabatrin therapy. The change of the medication to valproic acid plus ethosuximide resulted in seizure-freedom.

With respect to mental functions, the majority of the patients (61%) were severely or very severely retarded, 22% showed a moderate mental retardation and as many as 17% were within normal limits or only slightly retarded. Three of the four patients with cryptogenic infantile spasms were in the last group of patients, one child was moderately retarded.

DISCUSSION

Vigabatrin is a very promising alternative drug to ACTH or corticosteroids for treatment of children with infantile spasms. It has been shown to be very effective as add-on therapy and as a primary drug. In comparison with hormonal therapy, vigabatrin has an excellent safety profile.

The results after 3 months of vigabatrin add-on therapy in our prospective, open, uncontrolled three-centre trial in children with refractory infantile spasms are in accordance with the data from other reported trials[3–5], our results after short-term treatment have been published elsewhere[6]. All published studies document that vigabatrin seems to have considerably fewer and less severe side-effects than hormonal treatment. However, there are only a few data on the long-term effects of vigabatrin therapy on children with West syndrome.

In spite of treatment with ACTH or corticosteroids the long-term prognosis for children with infantile spasms remained poor, as has been confirmed in virtually all follow-up studies. These studies have reported a significant mortality rate of 5–20% and permanent mental retardation in about 80–90% of the patients. The probability of normal mental outcome for symptomatic seizures is very low (less than 15%), whereas it is much higher in those with cryptogenic spasms (about 40%)[2]. Unfavourable prognostic factors include poor initial response to treatment and persistent focal or multifocal inter-ictal EEG abnormalities, and this was true of the patients of this study.

Several methodological problems make it difficult to compare the long-term results of our study with those of hormonal therapy[19].

(1) Uncontrolled studies tend to exaggerate the possible benefits of the investigated drug. Few well-controlled prospective single- or double-blind hormonal studies have been performed, most studies have been retrospective. Our study is also an uncontrolled study.

(2) The number of patients that could be recruited for our study is rather small. In West syndrome there is a multiplicity of associated aetiological factors. Larger groups of patients are a prerequisite for comparable results, as all investigators agree that the most important predictor of treatment efficacy and long-term outcome is the underlying cause of the infantile spasms.

(3) The patients in the present study had been pretreated with various antiepileptic drugs and had turned out to be therapy-resistant against these drugs before vigabatrin was used. Because of this selection criterion the outcome is expected to be worse than in the studies with primary hormone treatment.

To compare the long-term outcome of vigabatrin with the standard therapy of ACTH or corticosteroids, two more recently published hormone studies by Riikonen and colleagues[20] and Glaze and colleagues[21] were chosen, as they contain detailed information with respect to mortality, psychomotor development and secondary epilepsies. The data are presented in Table 5.

In spite of the selection criterion of therapy resistance in our study the presented data demonstrate that the parameters of mortality rate, psychomotor development and occurrence of other epilepsies in this group of

patients are similar to those of the earlier hormone studies. The selection criteria of therapy resistance in our study may explain the high rate (72%) of children with focal or multifocal epileptic discharges after a mean observation time of nearly $5\frac{1}{4}$ years. However, the rate of secondary epilepsies is not higher than in the cited studies.

Three of the four patients from our study with cryptogenic West syndrome were mentally normal or only slightly retarded, and one of these children was moderately retarded. With vigabatrin all four patients became and remained seizure-free. This confirms the findings of all long-term studies that patients with cryptogenic infantile spasms have the better outcome.

One of the major questions is how long vigabatrin should have been given to responders. According to the study design with seizure-free patients with withdrawal of vigabatrin should not be started until after 2 years of treatment at the earliest. The mean duration of vigabatrin therapy in our patients who became seizure-free by this drug was $3\frac{3}{4}$ years (range: $1\frac{3}{4}$–$4\frac{3}{4}$ years), which would seem to be a long period of treatment. Several factors may have contributed to this: the fact that these children had not responded to other drugs, the high percentage of children with ongoing focal epileptic discharges and the lack of experience with this drug when the study was started (in 1989). Consequently this study does not provide a definite answer.

CONCLUSIONS

In children with infantile spasms vigabatrin seems to be a very effective drug in both short-term and long-term treatment. After a mean follow-up time of $5\frac{1}{4}$ years, 72% of 18 evaluable patients were seizure-free. The relapse rate of infantile spasms (14%) during vigabatrin therapy was low. Vigabatrin was well tolerated: in no child did vigabatrin have to be withdrawn because of an adverse event. The only remarkable side effect was irritability and hyperactivity in about 10% of the children. In those children who had been resistant to other drugs before the administration of vigabatrin, the long-term outcome with respect to other epilepsies and mental functions was similar to the data reported for hormonal treatment.

REFERENCES

1. Sorel, L. and Dusaucy-Bauloye, A. A propos de 21 cas d'hypsarrhythmia de Gibbs. Son treatment spectaculaire par l'A.C.T.H. *Acta Neurologica Belgica* 1958; **58**: 130–141.
2. Aicardi, J. Infantile spasms. In: *Epilepsy in Children* (Ed. J. Aicardi) 2nd Edition. *International Review of Child Neurology Series*. New York, Raven Press, 1994: pp. 18–43.
3. Chiron, C., Dulac, O., Beaumont, D. *et al.* Therapeutic trial of vigabatrin in refractory infantile spasms. *Journal of Child Neurology* 1991; **6** (Suppl. 2): 2S52–2S59.
4. Auerswald, G. Vigabatrin bei pharmakoresistenten Epilepsien im Kindesalter. *Aktuelle Neurologie* 1992; **19** (Sonderheft 1): 26–27.
5. Buti, D., Lini, M., Rota, M. *et al.* Vigabatrin (GVG) in infantile spasms (IS): results in 14 children. *Epilepsia* 1993; **34** (Suppl. 2): 94.
6. Siemes, H., Brandl, U., Spohr, H.-L. and Noll, S. Behandlung von BNS-Krämpfen mit Vigabatrin: Ergebnisse einer Add-on-Studie. *Aktuelle Neurologie* 1995; **22**: 97–103.
7. Vles, J.S.H., van der Heyden, A.M.H.G., Ghijs, A. and Troost, J. Vigabatrin in the treatment of infantile spasms. *Neuropediatrics* 1993; **24**: 230–231.
8. Appleton, R.E., Nicolaides, P. and Montiel-Viesca, F. Vigabatrin monotherapy for infantile spasms. *Epilepsia* 1995; **36** (Suppl. 4): 32.
9. Buti, D., Rota, M., Lini, M. *et al.* First-line monotherapy with vigabatrin in infantile spasms: longterm clinical and EEG evolution in 12 patients. *Epilepsia* 1995; **36** (Suppl. 3): S102.
10. Chiron, C., Dumas, C., Dulac, O. *et al.* Vigabatrin versus hydrocortisone as first-line monotherapy in infantile spasms due to tuberous sclerosis. *Epilepsia* 1995; **36** (Suppl. 3): S265.
11. Granström, M.L., Gaily, E. and Lindahl, E. Vigabatrin as the first drug in infantile spasms. *Epilepsia* 1995; **36** (Suppl. 3): S102.
12. Vigevano, F., Cilio, M.R., Faberi, A. *et al.* Vigabatrin versus ACTH in the treatment of infantile spasms. *Epilepsia* 1995; **36** (Suppl. 3): S265.
13. Aicardi, J., Sabrily, IS Investigator and Peer Review Groups, Mumford, J.P. Dumas, C and Wood, S. Vigabatrin as initial therapy for infantile spasms: a European retrospective survey. *Epilepsia* 1996; **37**: 638–642.
14. Appleton, R.E. and Thornton, L. Double blind comparison of vigabatrin vs placebo in newly diagnosed and previously untreated infantile spasms. *Epilepsia* 1996; **37** (Suppl. 5): 125.
15. Humbertclaude, V., Coubes, P.H., Rivier, F. *et al.* Efficacy of vigabatrin as first-line monotherapy in infantile spasms. *Epilepsia* 1996; **37** (Suppl. 4): 67.
16. Kwong, L. Vigabatrin as first line therapy in infantile spasms: review of seven patients. *Journal of Pediatrics and Child Health* 1997; **33**: 121–124.
17. Rufo, M., Santiago, C., Castro, E. and Ocana, O. Uso de monoterapia con vigabtrina en el tratamiento del sindrome de West. *Revue Neurologique* 1997; **25**: 1365–1368.
18. Chiron, C., Dumas, C., Jambaque, I., Mumforg, J. and Dulac, O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Research* 1997; **26**: 389–395.
19. Hrachovy, R.A. and Frost, J.D. Infantile spasms. *Pediatric Clinics of North America* 1989; **36**: 311–329.
20. Riikonen, R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. *Neuropediatrics* 1982; **13**: 14–23.
21. Glaze, D.G., Hrachovy, R.A., Frost, J.D., Kellaway, P. and Zion, T.E. Prospective study of outcome of infants with infantile spasms treated during controlled studies of ACTH and prednisone. *Journal of Pediatrics* 1988; **112**: 389–396.